CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20689

ADMINISTRATIVE DOCUMENTS

JUN 15 1998

Minutes of Meeting
June 2, 1998
NDA 20-689 Posicor (mibefradil dihydrochloride) Tablets
Discussion of Wording for Dear Doctor Letter and Press Release

Attendees:

FDA:

Robert Fenichel, M.D., Ph.D.	HFD-110	Deputy Division Director
Shaw Chen, M.D., Ph.D.	HFD-110	Medical Team Leader
Maryann Gordon, M.D.	HFD-110	Medical Officer
Gail White	HF-2	MedWatch (by telephone)
Lee Zwanziger, Ph.D.	HFD-006	Team Leader/Executive Secretariat Staff
Susan Cruzan	HFI-20	Public Affairs Specialist
Kathleen Bongiovanni	HFD-110	Project Manager

Hoffmann-La Roche:

Rudolph Lucek	Group Director, Drug Regulatory Affairs
Robert Pordy, M.D.	Director, Cardiovascular Clinical Sciences
Donald MacLean, Ph.D.	Vice President, Drug Regulatory Affairs
Valerie Suga	Director, Public Affairs

Background: On May 29, 1998, Hoffmann-La Roche agreed to voluntarily withdraw Posicor (mibefradil dihydrochloride) from the market in the near future. They asked for this meeting to discuss the wording of their letter (to physicians, pharmacists, nurse practitioners, physician assistants and other health care professionals) and the wording of their Press Release.

Meeting:

The group discussed the wording of the Dear Doctor letter (the wording will be used in the other letters), Hoffmann-La Roche's Press Release, and the wording of the FDA Talk Paper.

Hoffmann-La Roche plans to announce the withdrawal of the drug on Monday, June 8, at 2:00 a.m. (for their European customers) and 8:00 a.m. (for the U.S.). The FDA will also release our Talk Paper at that time. The firm will mail the letters (Dear Doctor, etc.) to the western half of the United States on Friday, June 5, and to the eastern half on Saturday, June 6. They will meet with the European regulatory authorities on June 3.

The firm noted that usually a Dear Doctor letter would include the current package insert for the subject product, but in this case the package insert has not been revised to include all relevant information, so they would like to omit it. Dr. Fenichel agreed with that plan.

Addendum:

After the meeting Robert Temple, M.D. (ODE 1 Office Director) reviewed the documents and made some additional changes. The marked-up copies of the firm's Dear Doctor letter and Press Release, and a copy the FDA Talk Paper that includes those revisions are attached.

Dr. Temple also agreed that in this case, it would make sense to omit the package insert from the letters. Ms. Bongiovanni checked with Ms. Baylor-Henry (Director, DDMAC), and she agreed that was acceptable.

Signature, minutes preparer: /S/
Kathleen F. Bonglovanni

6-15-98

Concurrence Chair: /S/
Robert R. Fenichel, M.D.

cc: ~~NDA 20-689~~
HFD-110
HFD-110/KBonglovanni
HFD-110/DRoeder
HFD-110/SBenton
HFD-006/LZwanziger
HFI-20/SCruzan
kb/6/3/98; 6/15/98.
R/D: MGordon/6/3/98; SChen/6/5/98; RFenichel/6/8/98.

JUN 2 4 1998

Memorandum of a Telecon between Hoffmann-La Roche and the FDA

Date: June 12, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Applicant: Hoffmann-La Roche

Subject: "Dear Doctor" Letter

Participants:

FDA

Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
David Roeder, HFD-110, Regulatory Health Project Manager

Hoffmann-La Roche

Rudolph Lucek, Regulatory Affairs
Isaac Kobrin, M.D., Clinical
Valerie Suga, Marketing

Background

On June 9, 1998, we received the attached e-mail from Dr. Michael Mullins regarding reports of adverse reaction associated with switching patients from mibefradil to other dihydropyridines without an adequate washout period. We communicated this information to the sponsor on that day. They indicated that they would instruct their detail staff to recommend to physicians that they wait several days after discontinuing mibefradil before beginning to dose another dihydropyridine or beta blocker. On June 12, 1998, the sponsor contacted us and requested a telephone conference to discuss the issuance of a "Dear Doctor" letter concerning this matter.

Telecon

The sponsor informed us that they have received reports of adverse events associated with switching patients from mibefradil to other drugs. They decided to issue a second "Dear Doctor" letter (attached). Dr. Fenichel said that he agreed with the main message of the letter, but he was concerned that by mentioning specific drugs, they run the risk of having missed one or more that could cause a problem. He favored a more conservative approach of saying that a washout period should be used in any case where one does not know that there is no danger of interaction. He also noted that the order of their bullets seemed unusual. If they were going to include this specific information, it would have been preferable to have listed the items in order of decreasing severity (i.e., beginning with #3 and ending with #4).

The firm pointed out that the time factor was extremely critical since they wished to issue the letter so that all physicians would have it by the weekend. Although it could be refined, if they spent time revising it, it could be significantly delayed.

Dr. Fenichel agreed that time was critical and that the letter could be issued as is.

Addendum

Dr. Temple dropped by shortly after this telecon. He was at least as unhappy as Dr. Fenichel with the proposed wording, but he conceded that timeliness might be the dominant issue. He indicated his intention to call Mr. Lucek.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Robert R. Fenichel, M.D., Ph.D.

dr/6-23-98/6-24-98

RD: RFenichel/6-22-98

cc: NDA 20-689
HFD-110
HFD110/DRoeder

JUN 25 1998

Minutes of a Telephone Conference Call Between Hoffmann-La Roche and the FDA

Date: May 29, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Applicant: Hoffmann-La Roche

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Kathleen Bongiovanni, HFD-110, Regulatory Health Project Manager
David Roeder, HFD-110, Regulatory Health Project Manager

Hoffmann-La Roche

Rudolph Lucek, Regulatory
Isaac Kobrin, M.D., Clinical

Background

We met with Hoffmann-La Roche on May 27, 1998 to discuss whether mibefradil should be taken from the market or re-labeled for second-line therapy (for hypertension and angina). This meeting was followed with an internal FDA meeting on May 29 (see minutes) in which it was decided that we would recommend that Roche remove mibefradil from the market and recall all distributed product. The purpose of this telephone conference call was to convey this decision to the applicant.

Teleconference

Dr. Temple summarized the decision from the FDA internal meeting. He noted that we sometimes do not insist that trials be done in refractory patients to support labeling for second-line therapy, but only in cases where we have reason to believe that the drug would work in that population. Mibefradil does not meet that criterion. Regarding hypertension, there are neither data nor rationale to support the use of mibefradil for second-line therapy. With regard to angina, it is implausible that a population could be identified and the risk controlled adequately to support general marketing of the drug for second-line therapy. Restricted distribution for second-line angina therapy is a possibility, but until that is worked out, the drug should be withdrawn from the market as soon as possible, preferably by the end of the following week. They should also recall all of the product that has already been distributed.

The applicant noted that the FDA response was similar to that from the European regulatory authorities. They plan to coordinate a world-wide action, so it would take a few days for them to make a decision. They said that they would let the FDA know of their decision by June 1, 1998.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/
Robert Temple, M.D.

dr/6-10-98/6-22-98/6-25-98

JUN 18 1998

Minutes of a Meeting

Date: May 1, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Applicant: Hoffmann-La Roche

Subject: Safety

Participants

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation 1
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
John Koerner, Ph.D., HFD-110, Pharmacologist
Emmanuel Fadiran, Ph.D., HFD-860, Biopharmaceutist
David Roeder, HFD-110, Regulatory Health Project Manager
Isaac Hammand, M.D., Ph.D., HFD-110, Medical Officer
Harold Davis, M.D., HFD-735, Medical Officer
Evelyn Rodriguez, M.D., M.P.H., HFD-735, Acting Branch Chief
Susan Lu, HFD-735, Postmarketing Safety Evaluator
David Graham, M.D., Medical Epidemiologist

Sponsor

Dr. Isaac Kobrin, Clinical
Dr. Robert Pordy, Clinical
Dr. Stephen Revell, Drug Safety
Dr. Roy Bullingham, Pharmacokinetics
Dr. Elisabeth Lindberg, Clinical
Mr. Charles Sabbah, Posicor Task Force Director
Mr. Rudolph Lucek, Regulatory
Dr. Gordon Tomasselli, Consultant
Dr. Craig Pratt, Consultant

Background

We met with the applicant on April 3, 1998 to discuss reports of torsades de pointes (TdP) in association with mibefradil use. In the course of the meeting, Hoffmann-La Roche argued that those cases of TdP that were not confounded by concomitant medications were probably due to an association of TdP with profound bradycardia and/or CHF. We asked that they provide documentation to support their argument and return for a follow-up meeting with the Agency. The applicant responded with a submission on April 14, 1998. A meeting was scheduled to discuss our response to that submission.

Meeting

Applicant's Presentation

The sponsor followed up their proposal for a labeling change that they had made in the April 3, 1998 meeting (contraindicating use with bepridil, all tricyclic antidepressants, thioridazine, pomozide, halofantrine and IV erythromycin). They proposed contraindicating the use of mibefradil with about 25 drugs (adding HIV protease inhibitors and anti-cancer drugs to the April 3 proposal). They would also strengthen the warnings to include drugs with any drug that has a large interaction and those with less profound interactions but that have small therapeutic margins. They also recommended that the labeling of drugs that interact with mibefradil be revised to include that information.

The applicant gave an overview of an educational campaign designed to increase awareness among health care workers and patients about possible drug interactions with mibefradil. This would include expanding their detailing campaign to include a wider physician base. They are also exploring the use of a card containing drug interaction information that would be carried by the patient, who would then be expected to show the card to pharmacists filling their prescriptions. Roche would provide incentives, possibly in the form of coupons, for the patients to use this card.

Discussion

Dr. Lipicky said that, although the drug is clearly effective at lowering blood pressure, we have to look very carefully at whether the adverse effects outweigh the benefit from blood pressure reduction. He believed, given the drug interaction and adverse reaction profiles of mibefradil, that it should not remain on the market. He noted, however, that not all at the Agency shared this belief.

Dr. Temple asked whether it was reasonable to expect health care workers to be able to keep track of the complicated dosing instructions that have to be made with this drug. Compliance will surely not be perfect. Roche needs to consider whether there is a real role for mibefradil. He thought there was little chance a good case can be made for a hypertension use; angina could be different. If the drug stays on the market, a patient package insert would be necessary.

Second line therapy for either claim does not appear at this time to be supportable because there are no data to show that it is effective in a refractory population and no reason to think it would be.

The applicant plans to submit the results from MACH I, a study in CHF patients, by mid-May. They asked that we wait to see the results of that study before making any decisions. They believed that this study could provide data regarding the proarrhythmic potential of mibefradil and possible benefit in patients with CHF. Dr. Lipicky agreed to review MACH I from a SAS dataset, a blank case report form with the SAS variable names, a brief written report such as a DSMB report, and the protocol with amendments.

Dr. Temple said that we are considering taking the issue to the July 1998 Cardio-Renal Advisory Committee meeting. Before doing so, however, we would need to do at least a brief

review of the MACH I data. The firm agreed to submit summary tables including mortality and cardiovascular morbidity data. Dr. Lipicky emphasized the importance of our being able to analyze the SAS data sets prior to taking it to the advisory committee meeting. It was agreed that the applicant will submit the data sets in addition to the summary tables, and the Division will look at the data and decide whether it is feasible to take the application to the advisory committee in July.

Minutes Preparation: /S/

David Roeder

Concurrence Chair: /S/

Robert Temple, M.D.

dr/5-21-98/5-29-98/6-18-98

RD: EFadiran/5-27-98
JKoerner/5-28-98
RFenichel/5-28-98
RTemple /6-18-98

cc: NDA 20-689
HFD-110
HFD-110/CSO
HFD-101/RTemple

JUN 16 1998

Minutes of a Meeting

Date: May 27, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Applicant: Hoffmann-La Roche

Subject: Safety

Participants

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation 1
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
John Koerner, Ph.D., HFD-110, Pharmacologist
Emmanuel Fadiran, Ph.D., HFD-860, Biopharmaceutist
David Roeder, HFD-110, Regulatory Health Project Manager
Isaac Hammand, M.D., Ph.D., HFD-110, Medical Officer
Doug Throckmorton, M.D., HFD-110, Medical Officer
Harold Davis, M.D., HFD-735, Medical Officer
Evelyn Rodriguez, M.D., M.P.H., HFD-735, Acting Branch Chief
Susan Lu, HFD-735, Postmarketing Safety Evaluator
Min Chen, HFD-735, Group Leader, Postmarketing Safety Evaluator
David Graham, M.D., HFD-735, Medical Epidemiologist
Susan Cruzan, HFI-20, Public Affairs Specialist
Lee Zwanziger, HFD-006, Policy Analyst

Sponsor

Dr. Isaac Kobrin, Clinical
Dr. Robert Pordy, Clinical
Dr. Roy Bullingham, Pharmacokinetics
Dr. Elisabeth Lindberg, Clinical
Mr. Charles Sabbah, Posicor Task Force Director
Mr. Rudolph Lucek, Regulatory
Dr. D. Zabrowski, Regulatory
Dr. D. Maclean, Regulatory
Dr. F. Bodin, Clinical
Mr. B. Brandstetter, Marketing
Dr. N. Neumann, Statistics

Background

The sponsor requested a meeting to discuss the results of the MACH I study in patients with congestive heart failure (CHF) and a proposal to relabel mibefradil for second line therapy.

Meeting

MACH I Results

The sponsor gave an overview of the MACH I study. They made the following conclusions:

- Mibefradil shows no benefit in CHF patients.
- Although the trial showed a negative (but statistically insignificant) trend in deaths, this trend disappears when patients receiving drugs that are known to cause torsades de pointes (TdP) are excluded from the analysis.
- Mibefradil can be used safely in patients with mild CHF if drugs that cause TdP are contraindicated.
- MACH I did not rule out the possibility that mibefradil has a proarrhythmic effect.

Dr. Temple noted that there are subsets in the study population (e.g., women) that had a higher incidence of adverse effects (death). The sponsor's explanation that concomitant medications were the cause of the problem does not necessarily explain the results. A closer analysis of the study would be necessary to come to any conclusion.

Labeling

The sponsor proposed revising the package insert to restrict the indication to second line therapy in hypertension and angina. They would also expand the CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS with regard to drug interactions. They would expect the drug to be used primarily by cardiologists, and they would focus an education program on that group.

Dr. Temple asked whether their approach was realistic and would be sufficient in light of the unusually complicated instructions for use that would have to be developed. Even if a patient was adequately screened for concomitant medications with the initial prescription, contraindicated drugs could be prescribed at a later date. It would be very easy to make mistakes.

In the case of hypertension, he said that he could not think of any situation in which second line therapy (i.e., in failures on other treatment) could be justified. The only benefit from antihypertensive therapy is the prevention of serious morbid events, so that a drug that is so difficult to use and has — even if it is only for that reason — a potential for causing morbid events does not seem acceptable.

Regarding angina, second line therapy is more of a possibility because patients do receive a symptomatic benefit and can perhaps reasonably make a decision to expose themselves to a known risk to achieve that benefit. Historically, however, we have not approved such drugs for

second line therapy unless they have been demonstrated to be effective in a refractory patient population. In the case of bepridil, the sponsor showed that bepridil was effective in patients who had not responded to diltiazem. Such studies have not been done for mibefradil.

The sponsor argued that mibefradil itself is not dangerous if used properly; therefore, second line therapy could be justified. Dr. Fenichel noted that the case of mibefradil is somewhat similar to that of thalidomide. It was also safe if used correctly, but one could not ensure its proper use in all cases, and the consequences of misuse were too severe to allow it to be marketed. (This has , of course changed, now that it has important, and unique, uses.) There are so many safe antianginal and antihypertensive drugs on the market that it is unlikely that mibefradil would provide a special benefit that would justify the risk.

Dr. Temple recommended that the sponsor suspend marketing until they are able to provide data to support their proposed labeling claims. The sponsor proposed that they be allowed to keep the drug on the market with a limited distribution system that would restrict use to patients with a known low risk. Dr. Stockbridge argued that at this point we cannot determine if a patient is at low risk. Dr. Temple agreed to convene an internal FDA meeting to decide what action should be taken and get back to the sponsor by June 1. The sponsor wished to take an action by the week of May 31.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/ 6/8/98
Robert Temple, M.D.

dr/5-28-98/6-16-98

RD: EFadiran/5-29-98
JKoerner/5-29-98
NStockbridge/6-3-98
MAGordon/5-29-98
SChen/5-29-98
RFenichel/6-1-98
RT/6-12-98

cc: NDA 20-689
HFD-110
HFD-110/DRoeder/SBenton
HFD-101/RTemple

JUN 23 1998

Minutes of Internal Meeting
May 29, 1998
NDA 20-689 Posicor (mibefradil dihydrochloride) Tablets

Attendees:

Janet Woodcock, M.D.	HFD-001	Director, CDER
Murray Lumpkin, M.D.	HFD-002	Deputy Center Director for Review Management
Robert Temple, M.D.	HFD-101	Director, Office of Drug Evaluation I
Rachel Behrman, M.D.	HFD-101	Deputy Director, Office of Drug Evaluation I
Linda Carter	HFD-101	Associate Director for Regulatory Affairs, ODE I
Florence Houn, M.D.	HFD-102	Deputy Director, Office of Drug Evaluation II
Raymond Lipicky, M.D.	HFD-110	Director, Division of Cardio-Renal Drug Products (by telephone)
Robert Fenichel, M.D., Ph.D.	HFD-110	Deputy Division Director
Paul Leber, M.D.	HFD-120	Director, Division of Neuropharmacological Drug Products
Shaw Chen, M.D., Ph.D.	HFD-110	Medical Team Leader
Maryann Gordon, M.D.	HFD-110	Medical Officer
Norman Stockbridge, M.D., Ph.D.	HFD-110	Medical Team Leader
Charles Ganley, M.D.	HFD-110	Medical Team Leader
John Koerner, Ph.D.	HFD-110	Pharmacologist
Steve Goldman, M.D.	HF-2	Associate Director for Medicine, MedWatch
Evelyn Rodriguez, M.D.	HFD-730	Acting Director, Div. of Pharmacovigilance & Epidem.
David Graham, M.D.	HFD-733	Medical Officer
Harold Davis, M.D.	HFD-733	Medical Officer
Lee Zwanziger, Ph.D.	HFD-006	Team Leader/Executive Secretariat Staff
Min Chen	HFD-735	Supervisory Pharmacist
Emmanuel Fadiran, Ph.D.	HFD-860	Biopharmaceutist
Susan Cruzan	HFI-20	Public Affairs Specialist
Natalia Morgenstern	HFD-110	Chief, Project Management Staff
David Roeder	HFD-110	Project Manager
Gary Buehler	HFD-110	Project Manager
Kathleen Bongiovanni	HFD-110	Project Manager

Background: The NDA for Posicor (mibefradil dihydrochloride) Tablets was approved on June 20, 1997 for the treatment of hypertension and angina. In December, 1997, Hoffmann-La Roche issued a Dear Doctor letter, describing new warnings on suppression of sinoatrial activity and severe bradycardia occurring with Posicor, and a new warning and contraindication concerning drug interactions and statin-induced rhabdomyolysis with Posicor and certain HMG-CoA reductase inhibitors.

Since that time many additional drugs (over 25) have been identified whose metabolism is inhibited by mibefradil's effect on CYP 450 3A4 and 2D6, including drugs that prolong the QTc interval, resulting in cases of torsade de pointes, and chemotherapeutic agents, resulting in increased toxicity.
Hoffmann-La Roche has recently proposed changing the package insert for mibefradil, limiting its use to those patients who have failed to respond optimally to, or are intolerant of, other antihypertensive or anti-anginal medications; however, the firm does not have data that show that mibefradil works in patients who have failed to respond optimally to these other therapies,

and there is some doubt as to whether there is a real population intolerant to all alternatives. In addition, the firm would add contraindications, warnings, and precautions about mibefradil's use with other drugs.

This meeting was called to discuss the firm's proposals and other alternatives, including whether mibefradil should be taken off the market.

Meeting:
Dr. Gordon gave a brief presentation on the drug's history

Use in Patients with Hypertension

There are no data to support mibefradil's effectiveness in patients who have failed to respond optimally to other therapies. Although mibefradil would presumably be effective in patients intolerant of other therapies, it is unlikely that there are patients with hypertension who cannot tolerate alternative drugs. The group agreed that it is not plausible that there is a population of patients with hypertension for whom this drug would offer an advantage over existing therapies. Therefore, whatever happened to the angina claim, there seemed no way mibefradil could continue to be indicated for hypertension.

Use in Patients with Angina

Angina seemed a potentially more viable claim, as there are patients who are not adequately treated by available therapy and who may have trouble tolerating negatively inotropic drugs (beta blockers and many calcium channel blockers). The MACH I trial was intended to see whether mibefradil could be used in patients with NYHA class III/IV CHF; that trial showed an adverse (though not significant) survival trend in the mibefradil group.

It was noted that the adverse events seen in patients taking mibefradil are probably not caused by mibefradil itself, but by its effect on the metabolism of other drugs used with it; therefore, in a controlled setting, one could perhaps control the rates of inappropriate concomitant therapy. There was a discussion about an alternative to withdrawal, allowing the firm to provide mibefradil, in a strictly-controlled, limited, named-patient distribution scheme, to patients with angina who are intolerant/non-responsive to other therapies. The group was divided, with some acknowledging the possibility that mibefradil might offer something unavailable elsewhere, and others concerned that the risks would outweigh the benefits and that the drug had not been shown to be effective in failure on other therapy. In the past where risks were severe, we have generally not allowed a drug to be labeled for use in a population non-responsive to existing therapies without having data to support a drug's efficacy in the non-responsive population. If the risk is less severe, however, we have considered such labeling, even without evidence of effectiveness in the population, based on the likelihood that individual responses vary.

Conclusions:

- We will call the firm and urge them to withdraw mibefradil from the market and to recall already distributed product, as soon as possible.

- The firm may choose to consider, as an alternative, allowing the drug to remain available in a strictly controlled, limited, named-patient distribution scheme, in patients with angina who are intolerant/non-responsive to other therapies.

Minutes Preparation: /S/ 6-23-98
Kathleen F. Bongiovanni

/S/
David Roeder

Concurrence Chair: /S/
Robert Temple, M.D.

Attachment

cc: NDA 20-689
HFD-110
HFD-101/RTemple/RBehrman/LCarter
HFD-110/KBongiovanni
HFD-110/DRoeder
HFD-110/SBenton
HFD-001/JWoodcock
HFD-2/MLumpkin
HFD-102/FHoun
HFD-120/PLeber
HF-2/SGoldman
HFD-730/ERodriguez
HFD-733/DGraham/HDavis
HFD-735/MChen
HFD-006/LZwanziger
HFI-20/SCruzan

kb/6-2-98
dr/6-19-98/6-22-98

D-F

JUN 9 1998

Memo to the File

Date: June 9, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subject: Dear Doctor Letter

The attached fax of the final "Dear Doctor" letter that was issued in December 1997 was never submitted officially to the NDA file. This memorandum with its attachment will serve as the record of that letter.

/S/

David Roeder
Regulatory Health Project Manager

attachment

cc: NDA 20-689
HFD-110
HFD-110/DRoeder

D.F

JUN 9 1998

Memo to the File

Date: June 9, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subject: "Dear Doctor" letter and press release

The attached faxes contain the final "Dear Doctor" letter and Hoffmann-La Roche's press release issued on June 8, 1998 regarding the removal of mibefradil from the market.

/S/

David Roeder
Regulatory Health Project Manager

attachment

cc: NDA 20-689
HFD-110
HFD-110/DRoeder

News Release

Roche

Contact: Valerie Suga
(973) 562-2174

For Immediate Release

ROCHE ANNOUNCES VOLUNTARY WITHDRAWAL OF POSICOR®

1-800-205-4611 Established to Answer MD/Consumer Questions

NUTLEY, NJ, June 8, 1998-- Roche today announced the voluntary market withdrawal of the anti-hypertensive and anti-anginal medication POSICOR (mibefradil) and is advising physicians to propose alternative therapies to their patients.

The company is taking this action based on evolving information concerning the potential for drug interactions which may occur when POSICOR is taken together with some other medications. The decision follows the analysis of the preliminary results of a three-year long-term study of POSICOR in congestive heart failure. The study demonstrated no overall difference between POSICOR or placebo when added to standard therapy in this patient population, but it provided further information on drug interactions.

In both hypertension and chronic angina pectoris, POSICOR has consistently proved to be effective and well tolerated, when used appropriately. However, the combination of POSICOR and some other commonly used drugs may increase the side-effects of these other medications.

In principle, drug interactions can be addressed by appropriate labeling; however, with respect to POSICOR, Roche believes that the complexity of such prescribing information would make it difficult to implement. As patient well-being is of highest priority to Roche, the company has decided to voluntarily withdraw the compound from the market.

Roche is working closely with the Food & Drug Administration to inform physicians and other health care professionals of its decision. Patients should not simply discontinue treatment with POSICOR; instead they should consult their physicians promptly about appropriate alternative therapy. In addition, patients should not add any new medication to their present treatment without consulting their physician. Information about the withdrawal for both healthcare professionals and consumers will be communicated via:

- A special hotline, 1-800-205-4611
- A nationally distributed letter to physicians, pharmacists, nurse practitioners, physician assistants and other health care professionals
- Communication of patient information through physicians, pharmacies, local/national constituency groups and community groups

# # #

N 20-084

FDA
TALK PAPER

JUN - 8 1998

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T98-33
June 8, 1998

Print Media: 301-827-6242
Broadcast Media: 301-827-3414
Consumer Inquiries: 800-532-4440

ROCHE LABORATORIES ANNOUNCES WITHDRAWAL OF POSICOR≥ FROM THE MARKET

Roche Laboratories of Nutley, NJ has announced that it is voluntarily withdrawing the heart drug, ≤Posicor≥ (mibefradil), from the market as a result of new information about potentially harmful interactions with other drugs.

In many cases, drug interactions can be addressed by appropriate labeling changes and public education, but due to the complexity of the prescribing information needed in this case, and seriousness of side effects, FDA and Roche agreed that it would be difficult to administer ≤Posicor≥ safely. The following may be used to respond to inquiries.

≤Posicor≥ is a calcium-channel blocker, chemically unlike the other approved products in this class. ≤Posicor≥ was approved in June of last year, to be used in the treatment of patients with hypertension and chronic stable angina.

≤Posicor≥ reduces the activity of certain liver enzymes that are important in helping the body eliminate many other drugs. Inhibiting these enzymes can cause some of these other drugs to accumulate in the body to dangerous levels.

When ≤Posicor≥ entered the market in August of 1997, its enzyme-inhibiting properties were described in the labeling. The labeling specifically listed three drugs (astemizole, cisapride, and terfenadine) that could be expected to accumulate to dangerous levels if ≤Posicor≥ was coadministered.

In December, after learning of several cases in which patients suffered serious adverse reactions after taking ≤Posicor≥ with one or more of the other drugs, FDA strengthened the labeling of ≤Posicor≥, and two more drugs (lovastatin and simvastatin) were added to the label's list of those that should never be coadministered with ≤Posicor≥. FDA also issued a public warning about this problem and the company issued a Dear Doctor letter to physicians.

From spontaneous reports and ongoing trials, FDA and Roche have continued to learn of adverse reactions related to coadministration of ≤Posicor≥ with several other drugs. At present, more than 25 drugs are known to be potentially dangerous if used with ≤Posicor≥ -- a number and diversity of drugs that cannot be practically addressed by standard label warnings.

Since ≤Posicor≥ has not been shown to offer special benefits (such as treating patients who do not respond to other antihypertensive and anti-anginal drugs), the drug's problems are viewed as an

unreasonable risk to consumers.

Patients now taking ≤Posicor≥ should not simply discontinue treatment because stopping medications can be risky. Instead, patients should promptly consult with their physicians about appropriate alternative therapy. In addition, patients now taking ≤Posicor≥ should not add any new medication to their current treatment without consulting their physicians.

Roche Laboratories is providing information in a "Dear Doctor" letter to physicians, pharmacists, nurse practitioners, and other health care professionals. Questions about the withdrawal of ≤Posicor≥ can be addressed to Roche's 24-hour hotline at 1-800-205-4611.

The following is a list of drugs that depend on the same liver enzyme as ≤Posicor≥ (mibefradil). Use of them in combination with ≤Posicor≥ could be dangerous.

Generic name	Trade Name
amiodarone	Cordarone
astemizole	Hismanal
bepridil	Vesture
cisapride	Propulsid
cyclosporine	Neoral, Sandimmune
cyclophosphamide	Cytoxan
desipramine	Norpramin
erythromycin	Erythrocin, Ilosone, others
etoposide	VePesid
flecainide	Tambocor
flutamide	Eulexin
halofantrine	Halfan
ifosfamide	Ifex
imipramine	Tofranil
lovastatin	Mevacor
mexiletine	Mexitil
pimozide	Orap
propafenone	Rythmol
quinidine	Cardioquin, Quinaglute, Quinidex, others
simvastatin	Zocor
tacrolimus	Prograf
tamoxifen	tamoxifen
terfenadine	Seldane
thioridazine	Mellaril
vinblastine	Velban
vincristine	Oncovin

For more information about this withdrawal of ≤Posicor, see:

"Dear Doctor" letter (Roche)

News Release (Roche)

FDA HOME PAGE

cc: NDA 20-669
HFD-110
HFD-110/DReader

DF

Minutes of a Meeting between Hoffmann-La Roche and the FDA MAY 22 1998

Date: April 3, 1998

Application: NDA 20-689
Posicor (mibefradil dihydrochlorde) Tablets

Sponsor: Hoffmann-La Roche

Subject: Safety Issues

Participants

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation 1
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
John Koerner, Ph.D., HFD-110, Pharmacologist
Ameeta Parekh, Ph.D., HFD-860, Biopharmaceutics Team Leader
Emmanuel Fadiran, Ph.D., HFD-860, Biopharmaceutist
David Roeder, HFD-110, Regulatory Health Project Manager
Khin Maung U, M.D., HFD-110, Medical Officer
Isaac Hammand, M.D., Ph.D., HFD-110, Medical Officer
Doug Throckmorton, M.D., HFD-110, Medical Officer
Harold Davis, M.D., HFD-735, Medical Officer
Evelyn Rodriguez, M.D., M.P.H., HFD-735, Acting Branch Chief

Sponsor

Dr. Isaac Kobrin, Clinical
Dr. Robert Pordy, Clinical
Dr. Stephen Revell, Drug Safety
Dr. Roy Bullingham, Pharmacokinetics
Dr. Elisabeth Lindberg, Clinical
Mr. Charles Sabbah, Posicor Task Force Director
Mr. Rudolph Lucek, Regulatory
Dr. Gordon Tomasselli, Consultant
Dr. Craig Pratt, Consultant

Background

We have recently received a number of reports of torsades de pointes in association with the use of mibefradil. We asked Hoffmann-La Roche to meet with us to discuss our concerns with the safety of mibefradil. Prior to the meeting, the sponsor faxed the attached position paper.

Meeting

Discussion Point #1: Rhabdomyolysis and Bradycardia

The mibefradil package insert was revised in December 1997 to strengthen warnings regarding mibefradil's suppression of sinoatrial node activity and the interaction between mibefradil and certain HMG CoA reductase inhibitors. The sponsor gave an overview of the incidence of these reports following the issuance of the "Dear Doctor" letter. It was their conclusion that the incidence has dropped with respect to the number of prescriptions.

The sponsor recommended revising the labeling to decrease the incidence of sinoatrial node suppression further. The package insert would say, "Avoid using mibefradil if pretreatment heart rate is below 60 bpm. Avoid using mibefradil 100 mg if heart rate is less than 60 bpm when on 50 mg." Dr. Temple questioned whether the word "avoid" was strong enough, but he said that the precise wording could be worked out at a later date.

Discussion Point #2: Torsades de Pointes

There have been a total of 14 cases (12 domestic) of torsades de pointes reported with the use of mibefradil since the product was launched. The sponsor noted that 6 of the 12 domestic cases were confounded by the presence of concomitant medications that are known to cause torsades by themselves, some of which would have their blood levels increased by mibefradil. The remaining six cases were not on suspect concommitant medications but all had heart failure, five were on digoxin and four of them developed torsades in association with significant bradycardia. The sponsor argued that profound bradycardia is known to be associated with torsades and that CHF was likely a contributing factor also. They did not believe that mibefradil was the direct cause of torsades in any of these cases.

The sponsor then showed reporting data to support their claim that the rate of torsades reports is actually dropping. FDA representatives questioned their assertion, however, arguing that from the way in which the data were presented, it was not clear that the incidence had actually declined.

The sponsor recommended strengthening the labeling to contraindicate concommitant use of mibefradil with the following drugs: bepridil, all tricyclic antidepressants, thioridazine, pomozide, halofantrine and IV erythromycin. Dr. Temple noted that it seemed very difficult for a physician to remember such complicated dosing instructions, and he wondered whether they would really follow labeling guidance.

The sponsor also argued that the results of their CHF study, MACH I, should shed some light on these safety concerns. Dr. Lipicky pointed out that this was not necessarily true for all uses of mibefradil. Even if mibefradil does cause torsades, it is possible that it also has an unrelated favorable effect on CHF patients. This positive effect could more than counter the negative effect of torsades, leading to an overall positive outcome for MACH I. Such an outcome would provide no assurance regarding the safety of mibefradil in the hypertensive population.

Conclusion

Dr. Temple laid out the following possible scenarios regarding the association of mibefradil with

torsades do pointes:

- If mibefradil is found to cause torsades by itself, it could not remain on the market for hypertension.

- If mibefradil is found to cause torsades by itself, it could possibly continue to be used to treat angina.

- If mibefradil is found to cause torsades in only special circumstances, and if instructions for use could be written so that it could be safely administered, it could remain on the market with revised labeling.

In order to ascertain if mibefradil does in fact cause torsades by itself, the Agency needs to review the documentation referred to by the sponsor regarding the association of torsades de pointes with bradycardia and CHF. The sponsor cautioned that the CHF connection was mostly hypothetical, but they will supply the Division with the publication shortly.

Even if mibefradil is not found to cause torsades by itself, Dr. Temple wondered whether a drug labeled with such extensive contraindications could be safety used; it interacts with too many other drugs that in themselves cause harmful effects (e.g., torsades, rhabdomyolysis, severe bradycardia, etc.).

Dr. Temple said that we will discuss the issue internally, followed by a meeting with the sponsor.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Robert Temple, M.D.

dr/4-10-98/4-27-98/5-19-98

RD: EFadiran/4-16-98
AParekh/4-17-98
JKoerner/4-20-98
MAGordon/4-20-98
SChen/4-20-98
RFenichel/4-20-98
RTemple/4-29-98

cc: ~~NDA 20-689~~
HFD-110
HFD-110/CSO

Attachment

SPONTANEOUS REPORTS OF TORSADE DE POINTES

Hoffmann- La Roche

April 3, 1998

Introduction

Since the launch of mibefradil (July 1997) and up to March 1998, over 300,000 patients (over 160,000 in US) started treatment with mibefradil. During this time period, 14 spontaneous reports of Torsade de Pointes (TdP) in patients on mibefradil therapy were identified by Roche Drug Safety. Twelve of the cases were reported from the US (exposure > 160,000), one from Germany (exposure > 80,000) and one from Switzerland (exposure > 20,000). The German case was not reported as TdP, but rather was diagnosed as such by Roche. Partial to complete information was obtainable by Roche for 13 cases. For one US case (93282) no information could be obtained by Roche or by the FDA. We were able to collect ECGs for 9 of the 14 cases and they were sent for evaluation to outside experts. For the other 5 cases we have been unable to obtain ECGs; therefore, one can not confirm the diagnosis of TdP. Detailed information on all of the cases is included in the attached appendix.

Thorough evaluation of the 13 cases for which information was available indicated that there were no instances of TdP in patients with isolated hypertension or angina patients without complicating co-morbidity or concomitant therapy with drugs known to be associated with TdP. Every documented case was associated with either a specific concomitant medication (7 cases) or CHF (6 cases), which are well known and well accepted causative factors in the genesis of TdP (Tables 1-3). Moreover, almost every patient had at least two additional confounding factors that could further contribute to the development of TdP.

The overall number of cases per month of TdP in association with mibefradil did not increase over time, despite the fact that there was a steady increase in exposure to the drug (Figure 1).

Demographics

All but one patient was elderly (12/13 ≥ 65, 11/13 ≥ 70 years). The only non-elderly patient (age 57 years) was a patient who had heart failure with a history of atrial fibrillation and mitral and aortic valve surgery. He was treated with digoxin, carvedilol, warfarin, doxazosin and amlodipine. There was no prolongation of QTc and the event was pause-related polymorphic ventricular tachycardia that was initiated by R on T in the presence of bradycardia (HR - 40 bpm).

There were six males and seven females. Out of the 12 patients for whom dosage information was available, three were taking mibefradil 50 mg, one 75 mg and eight were on 100 mg.

Cases in Patients on Drugs Known to Cause TdP

Seven patients took other drugs that are well known to be associated with TdP (Table 1):

- cisapride - 2
- bepridil - 1
- amiodarone - 1
- IV erythromycin - 1
- amitriptyline - 1
- nortriptyline - 1

All of these six medications not only are associated with TdP on their own, but they are also all metabolized by either Cytochrome P450 3A4 or 2D6. Mibefradil inhibits the metabolism of these two isoenzymes, and therefore when given concomitantly with mibefradil, the plasma concentrations of these other six drugs may be increased.

Several of these seven patients had additional factors that could facilitate the occurrence of TdP (Tables 1 and 3):

- 2 had congestive heart failure (CHF)
- 6 were on other drugs that lower heart rate (beta-blockers - 2, digoxin - 3, digoxin and a beta blocker - 1)
- 1 had documented hypokalemia (3.2 mmol/l)
- 2 were treated with furosemide.

Cases in Patients with CHF

The other six patients had CHF. These patients had additional reported factors that could promote the occurrence of TdP in CHF patients (Tables 1 and 3):

- 5 were on other drugs that lower heart rate (digoxin - 3, digoxin and a beta-blocker - 2)
- 1 had documented hypokalemia (3.4 mmol/l)
- 1 had documented hypokalemia (3.3 mmol/l) and hypomagnesemia (1.6 mmol/l)
- 5 were taking loop diuretics.

In four of the six CHF patients, the event of TdP was associated with bradyarrhythmic events. Two of the patients had slow junctional rhythm with sinus arrest, and two had severe bradycardia.

Post Marketing Observational Studies

In Germany, a post marketing observational study is currently being performed. Based on over 18,000 patients treated with mibefradil 50/100 mg for an average of 73.5 days there have been no reported cases of TdP. There have been a total of four deaths, none of which were arrhythmic (CVA, perforated abdominal aneurysm, cardiac failure X2).

Discussion

As indicated earlier, there were no cases of TdP in patients with isolated hypertension or uncomplicated angina pectoris. All patients were either on other drugs that could cause TdP or they had severe structural heart disease resulting in CHF. Moreover, in most patients there were other confounding factors that could contribute to the occurrence of TdP: drugs that lower heart rate and metabolic abnormalities.

The occurrence of TdP may be facilitated by very low heart rates in susceptible patients. As the heart rate lowering effect of mibefradil is dose related, it is not surprising that the majority of the reported cases of TdP occurred with the 100 mg dose of mibefradil. This applies even more when mibefradil is given concomitantly with other heart rate lowering drugs (11 out of 13 cases).

The smaller number of cases of TdP reported in Europe as compared to the US, despite similar exposure, may be a consequence of the following parameters:

- the stricter precautionary recommendations mandated by European Health Authorities in European labeling with regard to the use of mibefradil in the presence of low baseline heart rate and in combination with beta-blockers
- the presence of a mandated precautionary statement in European labeling concerning the concomitant use of mibefradil with drugs metabolized by CYP 450 3A4 or 2D6 which are known to prolong QT

As to the question of the potential contribution of mibefradil to the development of TdP in the six patients with CHF, a definite answer can only come from the results of the large placebo controlled study, MACH I (Mortality Assessment in Patients with CHF). Key results from this study of 2590 patients with 669 deaths will be available by May 15, 1998 (Table 4). CHF patients are the highest risk group for developing TdP, mainly because the action potential is prolonged and repolarization is delayed in heart failure (Tomaselli, et al: Sudden Cardiac Death in Heart Failure, The Role of Abnormal Repolarization, Circulation; 90:2534-2539, 1994). These patients often have metabolic abnormalities and are more likely to be prescribed drugs that could promote the development of TdP (e.g., antiarrhythmics, heart rate lowering drugs, diuretics).

Conclusion

1. There are no cases of TdP which occurred in patients with isolated hypertension and/or angina pectoris without complicating co-morbidity or concomitant therapy with drugs known to be associated with TdP.
2. All cases had confounding factors that are known to be associated with TdP.
3. Therefore, the degree of association of TdP to the administration of mibefradil is not established.
4. The analysis of MACH 1, a placebo-controlled study with 669 deaths, will clarify the degree of such associations by:

- translating the relationship of TdP to mortality
- allowing the analysis of the mortality consequence with coadministration of certain drugs (e.g., amiodarone) and facilitating conditions (e.g., hypokalemia, bradycardia)
- powerfully describing the association with mortality in patients with severe CHF

It is possible, however, that mibefradil could promote the occurrence of this arrhythmia through further lowering of heart rate in susceptible patients or through drug - drug interactions with compounds that either should not be given concomitantly with mibefradil or drugs whose dose should be decreased.

Based on these observations, it is planned to update the package insert with the following changes:

- stricter recommendation on the use of mibefradil in patients with low baseline heart rate and in patients on concomitant heart rate lowering medications (e.g. avoid use in patients with a pretreatment heart rate < 60 bpm and in patients on 50 mg of mibefradil do not increase the dose to 100 mg if heart rate is < 60 bpm)
- expand the drugs contraindicated with mibefradil to include specific drugs metabolized by CYP 2D6 and/or CYP 3A4 which prolong QT and with which an interaction with mibefradil is likely

As essential information concerning these issues will be available in mid-May following the analysis of the MACH 1 study, we would suggest that finalization of a revised package insert covering all outstanding issues be made at that time. In the interim, it is our proposal to work with the Division to draft all labeling changes not dependent on the MACH 1 results, so that upon the availability of these results immediate action can be taken.

Table 1:
Spontaneous Reports of Torsade de Pointes

Case No.	87899	92852	95976	96090	87634	90126	94490	86722	91557	84720	94061	96066	96070	83282
EXPERT DX	TdP	TdP	TdP	TdP				Poss TdP	Poss TdP	Poss TdP	TdP	TdP		
AGE	71	73	72	74	68		70	67	70	76	71	72	85	71
POSICOR(mg)	50	100	100	100	100	50		100	50	100	100	75	100	
CHF	-	X	-	X	-	-	-	X	X*	X	X	X	X	
IHD	X	X	X	X	-	X	-	-	X	X	X	X	-	
DRUGS THAT CAN CAUSE TdP**	X (Amio)	X (Ery)	X (Nort)	X (Amit)	X (Bep)	X (Cis)	X (Cis)							
Rx↓ HR***	1	1	2	1	1		1	2	2	1	1		1	
hypo K+			X							X	X			
hypo Mg+											X			
Loop Diuretics				X	X				X	X	X	X	X	

*LVH, LAH, mitrial and tricuspid insufficiency, pulmonary hypertension severe CAD.
** Bep=Bepridil, Cis=Cisapride, Amio=Amiodarone, Ery=Erythromycin IV, Nort=Nortriptyline, Amit=Amitriptyline.
*** Rx↓HR = Drugs that lower heart rate other than mibefradil.

Table 2:

Spontaneous Reports of Torsade de Pointes

14 Cases

9 EKGs available

5 EKGs not available

Case No.	Expert DX	Torsatogenic Factors
87899	TdP	Amiodarone / IHD / Rx ↓ HR
92852	TdP	Erythromycine IV / CHF / IHD / Rx ↓ HR
95975	TdP	Noitriptyline / IHD / ↓ K+ / Rx ↓ HR
96090	TdP	Amitriptyline / CHF / Rx ↓ HR / / Furosemide
89722	possible TdP	CHF / Rx ↓ HR
91587	possible TdP	CHF / IHD / 2 x Rx ↓ Hr / Furosemide
94720	possible TdP	CHF / IHD / ↓ K+ / Rx ↓ HR
94981	TdP	CHF / IHD / ↓ K+ / ↓ Mg+ / Rx ↓ HR
96066	TdP	CHF / IHD / Furosemide

Rx ↓ HR = Drugs that lower heart rate other than mibefradil.

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Table 3. TORSADE DE POINTES REPORTS CONFOUNDING FACTORS

	Other Confounding Factors			
Probable Cause for TdP	Tx ↓ HR	↓ K+	↓ mg +	Furosemide
Torsadogenic drugs (N = 7)	6	1	-	2
CHF (N = 6)	5	2	1	5
TOTAL (N = 13)	11	3	1	7

*Two patients had CHF

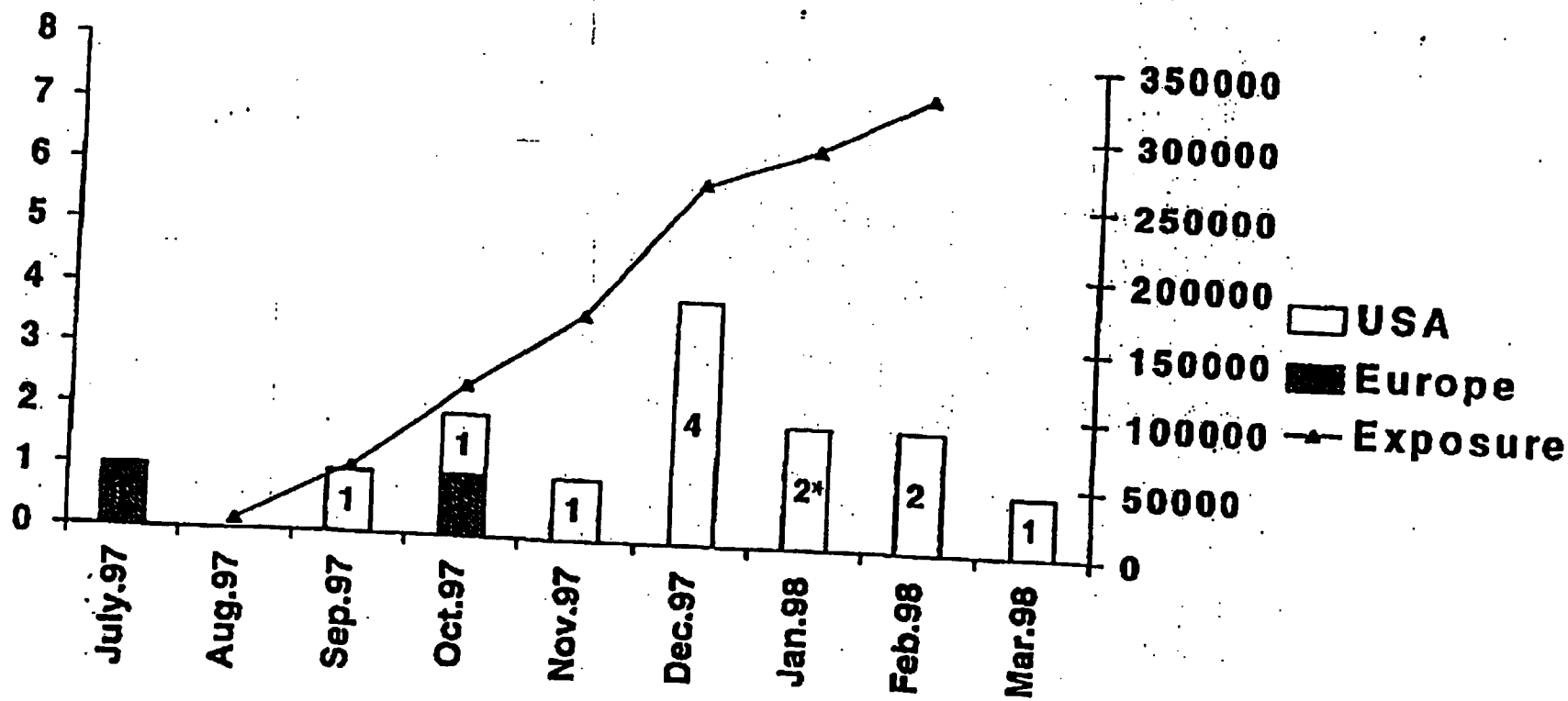
**One case with LVH, LAH, mitrial and tricuspid insufficiency, pulmonary HTN, severe CAD

Table 4: MACH-I
DATA AVAILABLE MID-MAY 1998

1. All Cause Mortality
2. CV Mortality
3. CV Morbidity
4. CV Mortality/Morbidity
5. CV Mortality and CV Morbidity in Subgroups
   - Concomitant treatments associated with drugs known to cause TdP (e.g., amiodarone)
   - QTc (Upper quartile)
   - Serum K+ (Lower quartile)
   - Gender
   - Age
   - HR < 45 bpm (at any time during treatment)
6. Serious AEs
   - Serious ventricular arrhythmias
   - Sudden death

Figure 1: Torsade de pointes reports

Occurrence over time vs exposure



*** Onset date unknown for 1 of these 2 cases, thus replaced by reporting date**

APPENDIX I: Spontaneous Reports of Torsade de Pointes

Entry Roche	MCN #	Country	Age/Sex	Dose	Significant Co-medications	Latency	Onset Date	Symptoms	Treatment	Other Factors Comments	ECG	Expert Opinion
30-Sep-97	87624	USA	68/M	50/100 mg/day	Bepridil Frusemide Atenolol	2 Weeks	28-Sep-97	Light-headedness Seizure	Unk	Reporter considered bepridil as cause of torsades bepridil and nifedipine apparently used for HT		
3-Oct-97	87899	CH	71/M	50 mg/day	Amiodarone Moduretic Digoxin Coumarin	2 Months	25-Jul-97	Malaise Palpitations Bradycardia 53 bpm	Unk	Hx of AF Stenosis R coronary artery. Pacing start 5/97 Amiodarone start 4/97	Y	TdP
3-Nov-97	89722	Ireland (reported from US)	57/M	50/100 mg/day	Cervedilol Digoxin Warfarin Doxazosin	3 Weeks	24-Oct-97	Bradycardia (40 BPM) Slow Junctional Rhythm Sinus Arrest Syncope VT/VF R on T	Pacemaker	Hx of AF with mitral and aortic valve disease (surgery 84), CHF. After cardioversion for VF was noted to have torsades. Hospitalised in Dublin QTc = 420 msec on admission	Y	Possible Torsades
1-Nov-97	90128	USA	Unk/F	50 mg/day	Cisapride (20 mg x 2)	Unk	Unk	Light-headedness Mobitz I heart block	Discont of medication	Recent increase in Cisapride dose IHD		
1-Dec-97	91567	USA	70/F	50 mg/day	Digoxin Gemfibrozil Metoprolol Fosinopril Frusemide	Unk	9-Dec-97	Dizziness Severe sinus bradycardia & bursts of VT	Unk	Recent CABG CHF (LVH, LAH, mitral and tricuspid insufficiency, pulmonary hypertension)	Y Strip before missing	Possible TdP
Jan-98	92652	USA	73/M	100 mg/day	Digoxin Insulin Thyroxine Pravastatin Erythromycin IV 500 mg tid x 4	69 days	5-Jan-98	Pneumonia Erythromycin was given for 1 - 2 days	Cardioversion Temporary pacemaker	Occured during hosp for pneumonia Pre-existing RBBB, CAD, CHD, CHF, DM, Parkinson.	Y	TdP

APPENDIX I: Spontaneous Reports of Torsade de Pointes

Entry Roche	MCN #	Country	Age/Sex	Dose	Significant Co-medications	Latency	Onset Date	Symptoms	Treatment	Other Factors Comments	ECG	Expert Opinion
20-Jan-98	93282	USA	71/F	Unk	Unk	3 Days	Unk	Unk	Unk	Minimal info. Pharmacist refusing to provide info. Claims that this has been reported to FDA with ECG's		
11-Feb-98	94459	USA	70/M	Unk	Cisapride Beta blocker	Unk	30-Dec-97	Unk	Posicor discont	Minimal info.		
16-Feb-98	94720	USA	76/F	100 mg/day	Isosorbide Omeprazole Digoxin Torasemide Triamcinolone Ipratropium Salbutamol Ciprofloxacin Insulin	6 Days	13-Dec-98	Syncope Seizures (?) associated with VT	Posicor discont	Abnormal EKG (repolarization disorder and prominent U waves) prior to onset of Posicor. COPD, CHF with severe LV dysfunction, chronic renal failure, Ulcer, DM Hypokalaemia (3.38 mmol/l) QTU = 600 msec Hypothyroidism	Y	TdP
18-Feb-98	94981	USA	71/F	100mg/day	Digoxin Thyroxine Frusemide Potassium Insulin	Unk	20-Dec-97	Asymptomatic bradycardia while waiting for routine treatment for chronic renal failure	Posicor discont Lignocaine	Ch Renal Failure CHF DM CAD, AF Breast Cancer Hypokalaemia (3.3) Hypomagnesaemia (1.6) QT = 600 msec	Y	TdP
9-Mar-98	95875	USA	72/F	100 mg/day	Nortriptyline Digoxin Atenolol Lorazepam Norfloxacin	8 Days	5-Mar-98	Chest pain Syncope Dizziness Bradycardia 50 bpm	Posicor discont Lignocaine Magnesium	Hx of AF Hypokalaemia (3.2 mmol/l) CAD Aortic stenosis and insufficiency Repolarization: double hump. (no previous ECG available)	Y	TdP

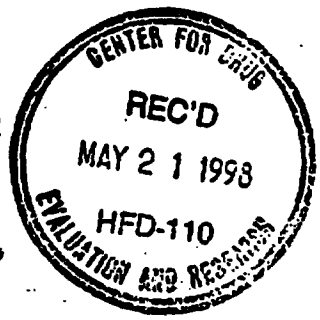
Entry Roche	MCN #	Country	Age/Sex	Dose	Significant Co-medications	Latency	Onset Date	Symptoms	Treatment	Other Factors Comments	ECG	Expert Opinion
12-Mar-98	98080	USA	74/F	100 mg/day	Amitriptyline Atorvastatin Digoxin Lisinopril Insulin Coumadin Furosemide	Unk	3-Feb-98	Syncope Pulmonary Edema	Unk	MI 3/4 years ago CHF AF Diabetes	Y	TdP
12-Mar-98	98070	USA	85/F	100 mg/day	Digoxin Furosemide Prednisone Glyburide	Unk	Unk	Lightheadedness Junction Rhythm 40 bpm Syncope	Pacemaker for AF alternating with sinus arrest & slow junctional rhythm	DM CHF Hypertension SSS (?) COPD		
10-Mar-98	98068	D	72/M	75 mg/day	Isosorbide Captopril Frusemide Aspirin Glibenclamide Buserelin	1 - 2 month	24-Oct-97	Syncope	Pacemaker for bradycardia (25 bpm)	CHF Chronic AF CAD Diabetes Prostate CA	Y	TdP

ORIGINAL

Roche

May 20, 1998

Division of Cardio-Renal Drugs Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
ATTN.: DOCUMENT CONTROL ROOM NO. 5002
1451 Rockville Pike
Rockville, Maryland 20852



Ladies and Gentlemen:

(SNC)

Re: NDA 20-689 - Posicor® (mibefradil dihydrochloride) Tablets
Pre-Meeting Submission for May 27, 1998 Meeting

In preparation for our meeting with the Division on May 27, 1998, at 11:00 am, we are herewith submitting the following information:

Enclosure 1 - Revised Package Insert

Enclosure 2 - Preliminary Results From The MACH I Study

At the subject meeting, we wish to review with you the preliminary results of the MACH I study and to discuss the proposed package insert revisions submitted herewith.

While the outcome of the MACH I study was statistically neutral, the data suggest that drug interactions may have been a major contributing factor in the overall outcome. To reduce the risk of potential drug interactions, the package insert has been revised to significantly strengthen and expand the contraindications, warnings and precautions concerning potential drug interactions with concomitant medications. Additionally, to increase the potential benefit of Posicor to patients, we wish to restrict the use of Posicor to those patients who can not be adequately controlled on, or can not tolerate other antihypertensive or anti-anginal medications and the package insert has been revised accordingly.

A strong medical need still exists for therapies which can effectively treat hypertension and angina pectoris. Posicor has been shown to be an effective and well tolerated medication for the majority of patients in these two indications. Particularly in angina pectoris, where there are few available treatment options, Posicor, given its beneficial heart rate lowering effect and lack of negative inotropism provides significant benefits to angina patients. Together, the aforementioned label revisions will markedly improve the benefit/risk of Posicor while providing a treatment option for those patients with no other alternatives.

ORIGINAL

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

If you should have any questions regarding this submission, please contact the undersigned.

Sincerely,

HOFFMANN LA-ROCHE INC.

Rudolph W Lucek

Rudolph W. Lucek
Group Director
Drug Regulatory Affairs

(973) 562-3688 (Phone)
(973) 562-3554/3700 (Fax)

Attachments
HLR No. 1998-1328

Desk Copy: Mr. David Roeder (12 complete copies)
Dr. Raymond Lipicky (1 complete copy)

MAY 12 1998

DIVISION OF CARDIO RENAL DRUG PRODUCTS
PERIODIC ADVERSE DRUG EXPERIENCE

NDA#20,689 Dated January 19, 1998
Reviewer: Maryann Gordon, MD

/S/ 5-12-98

This report covers the time period September 20, 1997 through December 19, 1997. There are 506 reports included in this submission. Of the 506 reports, 67 are serious initial, 6 are serious follow up, 426 non-serious initial, and 7 non-serious follow up. There were 144 initial and 78 follow up 15-day reports. At the time of this submission, a recent label change was made regarding the combination of mibefradil and beta blockers/other calcium channel blockers causing junction rhythms and/or heart blocker and the combination of mibefradil and certain statins causing rhabdomyolysis.

There were 10 deaths reported during this time period
-cardiac arrest following 2nd degree Mobitz type II heart block after 5 days of mibefradil,
-MI following 3rd degree heart block
-MI following concomitant use of simvastatin,
-MI following polymyositis
-ventricular fibrillation with CHF, rhabdomyolysis and hyperkalemia,
-ventricular fibrillation and asystole after 3 days of mibefradil
-bradycardia, no other information
-necrotic pancreatitis secondary to biliary lithiasis after 2 months on mibefradil,
-pneumonia after ileus,
-cerebral hemorrhage after 4 days of mibefradil.

Pharmacokinetic interaction study between mibefradil and a tricyclic antidepressant metabolized by cytochrome P450 2D6 (desipramine) is ongoing.

Need to investigate interaction between warfarin and mibefradil.

The table below shows the number of initial and follow up reports for the most worrisome events

Adverse event	initial	follow up
syncope	12	4
circulatory failure	1	0
convulsions	3	3
pancreatitis	2	1
torsades de pointes	4	0
ventricular fibrillation	2	2
cardiac arrest	6	4
ventricular tachycardia	1	0
hyperkalemia	3	2
hepatitis/jaundice	1	0

epistaxis/hematoma/hemorrhage /purpura	3	0
thrombocytopenia purpura	2	0
thrombocytopenia	1	0
renal failure	7	7
cerebrovascular disorder	2	0

The serious interactions with mibefradil and many other commonly used drugs as well as its ability to provoke torsades de pointes are being closely monitored. Adding contraindications to the package labeling with regards to concomitant use of certain statins, beta blockers and other calcium channel blockers had been completed and a "Dear Doctor" letter outlining these changes has been sent. Possible additional actions including removing mibefradil from the market are being considered.

cc
orig
HFD-110
HFD-110/CSO/SChen

FDA
TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

Correction: The 12/18/97 version of this statement could be read to say that Posicor should not be taken with any statin or with any immunosuppressant. That is inaccurate. Two of the statins, fluvastatin and pravastatin, are not significantly metabolized in the same way as the other statins. Mibefradil therefore would NOT be expected to have significant effects on fluvastatin and pravastatin blood levels or increase the risk of muscle injury. On the other hand, neither of the immunosuppressants tacrolimus and cyclosporine should be used together with Posicor and any statin. The statement concerning the 3-way combination should therefore read: The new label warns against the simultaneous use of Posicor, any statin and either of the immunosuppressants tacrolimus or cyclosporine. Also, the list of statins on page 3 should have included fluvastatin.

T97-65
Dec. 19, 1997

Susan M. Cruzan: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 800-532-4440

WARNING LABELING CHANGES FOR NEW HEART DRUG POSICOR

FDA is advising doctors about new warnings in the labeling of the drug Posicor (mibefradil), a treatment for hypertension and chronic angina. The new warnings provide additional information about two risks associated with the drug: extremely low heart rates, and, when Posicor is taken with certain cholesterol lowering drugs, a risk of muscle injury that can be life-threatening. The following may be used to respond to questions.

The new warning regarding low heart rates advises physicians against prescribing Posicor to patients at high risk of developing dangerously low heart rates. Such patients, especially older people, include those whose heart rates are already relatively low and those taking another drug that slows heart rate.

Posicor's risk of inducing excessively slow heart rates is similar to that of several other commonly used drugs, and was described in the labeling when the drug was first approved in June 1997. The new, strengthened warning was developed after FDA and the manufacturer, Roche Laboratories, of Nutley, NJ, received reports of dangerously lowered heart rates in about 20 patients who had taken Posicor. Many of the patients described in the reports had relatively low heart rates before starting Posicor, or had certain types of pre-existing heart disease that put them at high risk of such low rates. More than half of them were also taking another heart-rate-lowering drug, usually a beta-blocker. No deaths have been reported, but many patients became weak and lightheaded.

The second new warning states that Posicor should not be given to patients who are also receiving

lovastatin or simvastatin. These drugs used to lower cholesterol are known as statins. In addition, pending availability of further information, coadministration of Posicor with atorvastin or cerivastatin is strongly discouraged. Two of the "statins", fluvastatin and pravastatin, are not significantly metabolized in the same way as the other drugs. Mibefradil therefore would NOT be expected to have significant effects on fluvastatin or pravastatin blood levels or to increase the risk of muscle injury.

The new label also warns against the simultaneous use of Posicor, any statin, and either of the immunosuppressants tacrolimus or cyclosporine.

This new warning was added after the agency received 7 reports of drug-associated muscle injury among patients who had taken Posicor and simvastatin.

Drug-induced muscle injury is a known rare side effect of all of the statin cholesterol-lowering drugs including atorvastatin, cervistatin, fluvastatin, lovastatin, pravastatin, and simvastatin, and it seems to increase in frequency with increasing dose. Patients with drug-induced muscle injury usually experience nonspecific muscular symptoms (weakness, tenderness, and pain), but the most important consequences of injury are not muscular. The breakdown products of muscle can cause temporary or permanent damage to kidneys; and in severe cases, the heart can also be affected. Either of these complications can lead to death.

Although Posicor does not itself cause muscle injury, administration of Posicor interferes with the body's metabolism of lovastatin and simvastatin and may interfere with the metabolism of atorvastatin and cerivastatin. The observed incidence of muscle injury with coadministration of Posicor and simvastatin appears to be much higher than the incidence seen during treatment with simvastatin alone. The immunosuppressants tacrolimus and cyclosporine interfere with the elimination of all of the statins, and Posicor increases blood levels of cyclosporine and tacrolimus, so the three-way combination of Posicor, a statin, tacrolimus, or cyclosporine should also be avoided. Health care providers should report any adverse events related to Posicor to Roche Laboratories (800-526-6367) or to FDA. Reports may be submitted to FDA by telephone 800-332-1088), by fax (800-332-0178), or by mail using a postage paid MedWatch form from the back of the Physicians Desk Reference. The Medwatch report should be mailed to:

- MedWatch (HF-2)
- Food and Drug Administration
- 5600 Fishers Lane
- Rockville, MD 20857

BACKGROUND: POSICOR LABELING CHANGES

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FDA HOME PAGE

OF

JAN 13 1998

Minutes of a Meeting Between The FDA and Hoffmann-La Roche

Date: November 26, 1997

Application: NDA 20-689/S-001
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subject: Labeling

Participants

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation 1
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director, Division of Cardio-Renal Drug Products
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
David Roeder, HFD-110, Regulatory Health Project Manager
David Orloff, M.D., HFD-510, Medical Team Leader
Harold Davis, M.D., HFD-733, Medical Officer
Susan Lu, HFD-735, Epidemiology Reviewer
Emmanuel Fadiran, Ph.D., HFD-110, Biopharmaceutist

Sponsor

Rudolph Lucek
Isaac Kobrin, M.D.
Robert Pordy, M.D.
Henry Solomon, M.D.
Roy Bullingham, Ph.D.
Charles Sabbah
Daniel Zabrowski, Ph.D.
Michael Carter, M.D.
Craig Brater, M.D.

Background

Roche submitted a supplement, S-001, that initially provided for labeling changes regarding cardiac rhythm disturbances associated with the use of mibefradil. They agreed to write a "Dear Doctor" letter warning physicians of this adverse event. Before the "Dear Doctor" letter could be finalized, however, we received eight reports of rhabdomyolysis in association with the concomitant use of mibefradil and simvastatin. It was decided that this serious adverse drug interaction should also be added to the warnings in the package insert and included in the "Dear Doctor" letter. An internal FDA meeting was scheduled to discuss the content of the revised labeling and to coordinate the Agency's actions to accompany the "Dear Doctor" letter. An internal meeting was held on November 25, 1997 to discuss this issue (see minutes).

The sponsor requested a meeting with the Agency to discuss the labeling and "Dear Doctor" letter.

Meeting

Discussion Point #1: Interaction of mibefradil with simvastatin and lovastatin

The sponsor argued that although mibefradil interacts differently with simvastatin and lovastatin than with the other statins, and that a warning about simvastatin and lovastatin should appear in the labeling, their coadministration with mibefradil should not be contraindicated. They claimed, based on a pharmacokinetic (PK) interaction study, that the lowest dose of simvastatin could be safely administered with mibefradil. Dr. Temple disagreed. He did not believe that the results of the PK study were conclusive or could account for variability, and he believed that there would be considerable risk in administering mibefradil with any dose of simvastatin. Given the other choices of calcium channel blockers and statins, there is no reason to take such a risk. He also pointed out that if we recommend coadministration of mibefradil with low doses of simvastatin, many physicians would be likely to raise the dose if a greater effect is needed.

Discussion Point #2: Interaction of mibefradil with atorvastatin and cerivastatin

The sponsor argued that the interaction of mibefradil with atorvastatin and cerivastatin are materially different from the interaction with simvastatin and lovastatin. Atorvastatin and cerivastatin both have active metabolites, which would fall when parent compound rose; this would be expected to lead to less of a problem from a 3A4 inhibitor like mibefradil. They also pointed out that cerivastatin and atorvastatin have relatively high bioavailability so that inhibition of thier metabolism could not give rise to excessive elevations of plasma levels. They acknowledged that the bioavailability of atorvastatin is not as high (about 10% for the parent compound and 30% for the active metabolite) but still thought the risk was lower. They also have published (abstract) data on the interaction of erythromycin with atorvastatin and cerivastatin. Erythromycin had only small effects on the pharmacokinetics of either drug.

Dr. Temple agreed that the higher bioavailability and active metabolite arguments had merit but cautioned that we still have very little data so far. He agreed to consider removing the contraindication to coadministration of mibefradil with atorvastatin and cerivastatin and to instead include a warning against the concomitant use of these drugs until more is known.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/ 1/13/98
Robert Temple, M.D.

dr/12-4-97/12-30-97/1-5-97

DF

JAN 13 1998

Minutes of a Telephone Conference Call

Date: October 31, 1997

Application: NDA 20-689
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subject: Labeling and "Dear Doctor" Letter

Participants

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation 1
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director, Div of Cardio-Renal Drug Products
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
David Roeder, HFD-110, Regulatory Health Project Manager

Sponsor

Isaac Kobrin, M.D.
Robert Pordy, M.D.
Robert Shehan
Rudolph Lucek
Craig Pratt, M.D. (Consultant)

Background

Hoffmann-La Roche met with the Division on October 22, 1997 to discuss the recent cases of rhythm disturbances associated with the use of mibefradil. After the meeting, Dr. Lipicky discussed the issue with Dr. Temple. Dr. Temple recommended that the sponsor issue a "Dear Doctor" letter in addition to informing physicians via the detail force. Mr. Roeder conveyed this request to the sponsor, who then requested a telephone conference with Dr. Temple to discuss the issue.

Discussion

The sponsor argued that the problem is primarily one of some physicians using the drug in the wrong patient population. They believed that their planned educational program could adequately inform health care professionals to the proper use of mibefradil. They did not believe that a "Dear Doctor" letter would be necessary.

Dr. Temple stated that he felt any important change such as this should be accompanied by a "Dear Doctor" letter and the letter should be issued as soon as possible. Given the risk of death, it would not be appropriate to wait to see if the educational program is working before the

"Dear Doctor" issues. He also said that the letter should be written as "an important new Warning", not as "important new prescribing information." A draft of the letter should be submitted to the FDA for review before it is issued.

The sponsor asked if they could mention in the letter that similar effects are seen with verapamil and diltiazem. Dr. Temple said that they need to be careful not to undermine the warning through this kind of statement. We haven't seen the data on verapamil and diltiazem yet, and it would have to be reviewed. He said that we would look into the data on these other drugs. If the events here are common to a class of agents, that could be pointed out.

Dr. Temple asked about the frequency of this adverse event in the MACH 1 study. The sponsor replied that there have been 13 cases of AV block reported to date (at least several of them have been determined to be junctional rhythm). Dr. Temple suggested that they assemble a package containing the incidence of AV block and/or junctional rhythm in MACH 1 and compare this with the large diltiazem and verapamil trials.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/ 1/13/98
Robert Temple, M.D.

dr/11-28-97/12-30-97/1-5-97

RD: MAGordon/12-8-97
SChen/12-8-97
RFenichel/12-8-97
RTemple/12-31-97

cc: ~~NDA 20-689~~
HFD-110
HFD-110/CSO

DF

DEC 2 5 1997

JAN 1 2 1998

Minutes of an Internal FDA Meeting

Date: November 25, 1997

Application: NDA 20-689/S-001
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subject: Labeling and "Dear Doctor" Letter

Participants

Murray Lumpkin, M.D., HFD-002
Lee Zwanziger, HFD-006
Janet Norden, HFD-40
Robert Temple, M.D., HFD-101
Robert Fenichel, M.D., Ph.D., HFD-110
Shaw Chen, M.D., Ph.D., HFD-110
Maryann Gordon, M.D., HFD-110
David Roeder, HFD-110
Barry Poole, HFD-210
David Orloff, M.D., HFD-510
Susan Lu, HFD-735
Emmanuel Fadiran, Ph.D., HFD-860
Stephen Goldman, M.D., HF-2
Susan Cruzan, HFI-20

Meeting Objective: To come to a consensus on the Agency's response to recently reported serious adverse events with Posicor.

Background: Roche submitted a supplement, S-001, that initially provided for labeling changes regarding cardiac rhythm disturbances associated with the use of mibefradil. They agreed to write a "Dear Doctor" letter warning physicians of this adverse event. Before the "Dear Doctor" letter could be finalized, however, we received eight reports of rhabdomyolysis in association with the concomitant use of mibefradil and simvastatin. It was decided that this serous adverse drug interaction should also be added to the warnings in the package insert and included in the "Dear Doctor" letter. An internal FDA meeting was scheduled to discuss the content of the revised labeling and to coordinate the Agency's actions to accompany the "Dear Doctor" letter.

Discussion Point #1: Labeling for interactions between mibefradil and the "statins"

The discussion focused on how the package insert should address the coadministration of mibefradil with the various approved statins. All of the reported cases of rhabdomyolysis with mibefradil involved concurrent administration with simvastatin. Mibefradil is a significant 3A4 inhibitor (and is so labeled) and blocks the metabolism of simvastatin via the CYP3A4 metabolic pathway, greatly increasing blood concentrations and increasing the risk of rhabdomyolysis, a rare event associated with the use of all statins and apparently dose-related.

Although no cases of rhabdomyolysis have been reported with the coadministration of mibefradil and the three other statins that are dependent on CYP3A4 metabolism (lovastatin, cerivastatin and atorvastatin), there is reason to be concerned about the use of mibefradil with these drugs. Lovastatin is metabolized similarly to simvastatin and is known to show a great increase in blood levels with itraconazole, a potent 3A4 inhibitor. Atorvastatin and cerivastatin are metabolized by 3A4 but form active metabolites so that the effect of 3A4 inhibition on total statin activity may be less. Erythromycin has been shown not to have a large effect on statin blood levels for both drugs. The other statins, pravastatin and fluvastatin, are either not metabolized by CYP3A4 or have alternate metabolic pathways.

Agreements

• Simvastatin and lovastatin: It was agreed that there are sufficient data to conclude that concurrent use of mibefradil with simvastatin and lovastatin should be contraindicated.

• Atorvastatin and cerivastatin: It was less clear as to whether the concurrent use of mibefradil with these drugs should be contraindicated. Roche has presented limited data to support their argument that mibefradil is unlikely to interact with atorvastatin or cerivastatin in such a way as to increase the risk of rhabdomyolysis, and available data with erythromycin (abstracts) are reasonably reassuring. It was decided, however, that too little is known and that, until more evidence is available, the concurrent use of mibefradil with these drugs should be discouraged.

• Pravastatin and fluvastatin: It was agreed that the labeling should not recommend against the use of mibefradil with pravastatin or fluvastatin. There are adequate data available to conclude that mibefradil does not inhibit the metabolism of fluvastatin and that CYP3A4 inhibitors have only a minor effect on the plasma levels of pravastatin.

• Warnings: It was agreed that the Warnings section should describe the interaction of mibefradil with the statins and the risk of rhabdomyolysis, but that it should not mention that the specific cases reported to date and the particular drug (simvastatin) that was associated with them because this was likely to change, and the information would likely become obsolete in a short time. It was appropriate, however, to mention simvastatin as the associated drug in the "Dear Doctor" letter because that would reflect current data.

Discussion Point #2: "Dear Doctor" letter, talk paper and other ways of disseminating this information

Agreements

• The sponsor has submitted, and DDMAC has reviewed and commented on, a draft of the "Dear Doctor" letter. The sponsor will meet with the Dr. Temple and HFD-110 on November 26 to discuss it. Our goal is to have the letter issue by December 1 or 2.

• Dr. Fenichel had prepared a draft talk paper. The Press Office will work with him to have it ready for release when the "Dear Doctor" letter issues.

• Dr. Goldman will arrange a telephone conference for the day after the "Dear Doctor"

letter issues with the following medical organizations:

American College of Cardiology
American Heart Association
American College of Physicians
American Academy of Family Physicians
American Diabetes Association
American Society of Hypertension
American Society of Internal Medicine
American Society of Health-System Pharmacists

- The talk paper will be adequate for use by OTCOM.

- Mr. Roeder will find out how widely mibefradil is marketed internationally so that Dr. Lumpkin can discuss the issue with foreign regulatory agencies.

Action Items

- Drs. Fenichel and Orloff will draft labeling according the agreements of this meeting.

- Dr. Fenichel will work with Susan Cruzan to finalize a talk paper.

- Dr. Temple and HFD-110 will meet with Roche on November 26 to discuss the labeling and "Dear Doctor" letter.

- Dr. Goldman will arrange a telephone conference with the appropriate medical organizations to brief them on this issue.

- Mr. Roeder will update Dr. Lumpkin on the foreign marketing history of mibefradil so that he can communicate with the foreign regulatory authorities.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Murray Lumpkin, M.D.

dr/11-28-97/12-15-97

JAN 12 1998

Minutes of a Meeting between Hoffmann-La Roche and the FDA

Date: October 22, 1997

Application: NDA 20-689/S-001
Posicor (mibefradil dihydrochloride) Tablets

Sponsor: Hoffmann-La Roche

Subjects: 1) Cardiac Rhythm Disturbances and Mibefradil
2) Development of Mibefradil for Treating Atrial Fibrillation

Participants

FDA

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Natalia Morgenstern, HFD-110, Supervisory Project Manager
David Roeder, HFD-110, Regulatory Health Project Manager
Harold Davis, M.D., HFD-733
Min Chen, HFD-735

Sponsor

Robert Pordy, M.D., Clinical
Isaac Kobrin, M.D., Clinical
Rudolph Lucek, Regulatory
Craig Pratt, M.D., Consultant

Background

On September 23, 1997, the Division received a "Changes Being Effected" labeling supplement for changes primarily regarding cardiac rhythm disturbances associated with mibefradil. Also, a minor change was made to the PRECAUTIONS section to reflect a single case of rhabdomyolysis. No data were submitted to this supplement. On October 1, 1997, the project manager called the sponsor and requested supporting documentation for labeling changes. He also recommended that, since these labeling changes were significant and the Division may recommend revisions, the firm should consider waiting for Division comment prior to making final printed labeling.

The Division requested a meeting with the sponsor to discuss the actions that should be taken regarding these reports of cardiac rhythm disturbances. The sponsor asked to discuss their plans for developing mibefradil for treating atrial fibrillation.

Meeting

Discussion #1: Clinical meaning of the reported cardiac rhythm disturbances

The sponsor obtained follow-up information on as many of the reported cases as possible. Although these case were reported as AV block, upon closer examination, it appears that they are actually cases of junctional rhythm. The sponsor argued that these cases were actually the result of administering mibefradil to an inappropriate patient population. The patients were generally elderly women who already had abnormally slow heart rates, in some cases due to the administration of other bradycardic drugs such as beta-blockers. These patients should not have been given mibefradil. It also appears that in a number of these cases, mibefradil merely unmasked previously existing sick sinus syndrome, a condition for which mibefradil is already contraindicated.

Agreement: Dr. Lipicky agreed with the sponsor's conclusion.

Discussion Point # 2: Action Plan

In addition to labeling revisions, the sponsor proposed to implement a physician education program to target the misuse of bradycardic agents such as mibefradil in a frail elderly population. They plan to contact all cardiologists in the U.S. within 8 weeks. This program would go beyond the mibefradil cases to educate physicians to the proper use of all bradycardic agents.

In addition to the educational program, the sponsor plans to carefully monitor all reports of additional cases for two months to ensure that the event rate declines. The education program would begin in mid-November, and the monitoring program would start in January.
Dr. Lipicky was concerned that the monitoring results would be inconclusive because physicians would be less likely to report adverse events that are expected. The sponsor assured him that, as part of their educational program, they will encourage physicians to report all cases.

Agreement: Dr. Lipicky said that the sponsor's proposal sounds reasonable, but he would have to discuss it internally before he could reach a conclusion. Labeling revisions will be drafted and sent to the sponsor within 1 week. Dr. Fenichel recommended that the sponsor determine the background rate for reports of this nature so as to determine a target rate of events following the educational program.

Discussion Point #3: Development of mibefradil for treatment of atrial fibrillation

The sponsor presented an outline for a development program for the treatment of atrial fibrillation. Dr. Lipicky made the following comments:

- The sponsor could measure symptom benefit by telemetry. The primary endpoint could be apical heart rate, and the secondary endpoint could be telemetry.

- A placebo controlled trial would be necessary. A positive controlled trial with digoxin would not be appropriate because the effectiveness of digoxin for the proposed endpoints is not known.

- A single trial could be adequate for approval only if the p value is much smaller than 0.05.

- If the sponsor wishes to get a claim for a secondary endpoint, they must power the trial to show an effect on that endpoint.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/
Raymond Lipicky, M.D.

Enclosure

dr/11-28-97/12-17-97

RD: MGordon
SChen
RFenichel

cc: NDA 20-689
HFD-110
HFD-110/CSO

DF

JAN 6 1998

Minutes of a Meeting

Meeting Date: December 10, 1997

Applications: NDA 20-689
Posicor (mibefradil dihydrochloride)

Sponsor: Hoffman-La Roche Inc.

Purpose of Meeting: Discuss labeling and Dear Doctor letter regarding changes to the Contraindications and Warnings sections

Attending:

Hoffman-La Roche:

Dr. Isaac Kobrin	Global Clinical Director
Dr. Robert Pordy	U.S. Clinical Director
Dr. Henry Solomon	Clinical Medical Director
Dr. Attila Kursun	Clinical Medical Director
Dr. Frederick Bodin	Worldwide Medical Marketing Director
Mr. Robert Sheehan	Marketing Director
Ms. Susan Benner	Product Director
Mr. Rudolph Lucek	Regulatory Affairs

FDA:

Robert Temple, M.D.	Director, ODE I, HFD-101
Robert Fenichel, Ph.D., M.D.	Deputy Director, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
David Orloff, M.D.	Medical Officer, HFD-510
Emmanuel Fadiran, Ph.D.	Biopharmaceutist, HFD-860
Diana Willard	Regulatory Health Project Manager, HFD-110

Meeting Chair: Robert Fenichel, Ph.D., M.D.

Meeting Recorder: Diana Willard

Background: This teleconference was scheduled in order to finalize the wording in both the package insert and the "Dear Doctor" letter regarding Posicor's interaction with statins.

Meeting: The meeting began with a discussion of the facsimile transmission (FAX) received from Hoffman-La Roche on December 10, 1997 (Attachment 1) regarding the **WARNINGS** section of the Posicor labeling. The changes agreed to in the wording proposed by Hoffman-La Roche are noted on the attached FAX.

The changes made and agreed to in the **WARNINGS**/Drug Interactions - Cyclosporine/ Tacrolimus and HMG CoA Reductase Inhibitor section are noted on page 3 of Attachment 2.

The one change made and agreed to in the "Dear Doctor" letter is noted in Attachment 3.

The Agency noted that a Talk Paper will be going out soon after the "Dear Doctor" letter issues. Hoffman-La Roche will have an opportunity to preview the Talk Paper before it issues. Although Hoffman- La Roche can not have any control over the final wording for the Talk Paper, constructive criticism is welcome. The Talk Paper will probably be posted on the CDER Website. Hoffman-La Roche stated that the "Dear Doctor" letter will issue early next week. Dr. Temple stated that the entire label should be appended to the letter.

Addendum

Subsequent to the teleconference, Dr. Fenichel and Ms. Willard spoke with Mr. Rudolph Lucek regarding the **PRECAUTIONS/Drug Interactions/EFFECTS OF MIBEFRADIL ON THE PHARMACOKINETICS OF OTHER DRUGS** section. Mr. Luck agreed that the Cyclosporine section would be moved to beneath the HMG COA Reductase Inhibitors section and changed to state:

Cyclosporine and tacrolimus: (see WARNINGS).

Signature, Minutes Preparer /S/ Diana Willard

Concurrence, Meeting Chair /S/ Robert Fenichel, Ph.D., M.D.

cc: original file
HFD-110
HFD-101/RTemple
HFD-110/DRoeder
HFD-110/DWillard
HFD-110/SBenton

Drafted: 12/19/97
RD: Temple 12/30/97
Fenichel 12/23/97
Gordon 12/22/97
Fadiran 12/22/97

OCT - 8 1997

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/ODE-I/DIV CARDIO-RENAL DRUGS

Date: 09/29/97
To: Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs
Through: R. Lipicky, M.D., Director, DCRDP, HFD-110
From: Shaw T. Chen, M.D., Medical Group Leader, HFD-110 /S/

Subject: Medical Letter Draft on Mibefradil

The Division was requested to comment on the Medical Letter draft issue announcing the approval of mibefradil.

Again as the other Medical Letter articles we have reviewed, this monogram is not an in-depth account of the approval basis for mibefradil. My specific comments are summarized as follows:

1. In the section on mechanism (Lines 9-16), a disclaimer on the clinical meaning of preferential T-channel blockade by mibefradil should be added here (as that stated at the end of the draft).
2. In the description of efficacy data, the draft appeared to be limited to published reports, but the information presented appeared to reflect that of package insert.
3. Reference to comparative claims, either in efficacy or safety, (Lines 27-32 and others) can hardly be endorsed by the Agency. Relative potency is meaningless without comparing the entire dosage range and overall benefit/risk assessment.
4. We do not believe that mibefradil's claim on coronary artery dilation (Lines 65-66) can be substantiated regulatory-wise.

cc:
ORIG: NDA- 20-689
HFD-110
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